## REMARKS

Claims 18 and 25-35 are pending in the application. Claims 1-17 and 19-24 were previously canceled. Claims 18 and 25-35 are rejected under 35 U.S.C. § 103(a) as being unpatenable over Wedeking et al. (U.S. Patent No. 6,093,382; hereafter "Wedeking") in view of Sinkule et al. (European Patent Application No. 0282057; hereafter "Sinkule"). Claims 18, 25-28, and 30-35 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Wedeking in view of Goldenberg (U.S. Patent No. 5,698,178; hereafter "Goldenberg"). Applicants address each of these rejections below.

### The Claimed Invention

Claim 18 is directed to a method of targeting a radionuclide to a malignant cell within a subject, where the malignant cell expresses a tumor associated antigen and expresses folate binding protein. This method involves (i) coupling an antibody, antibody fragment, or antibody construct having affinity for the tumor associated antigen to at least one non-cytotoxic folate to form a dual binding conjugate, (ii) coupling the radionuclide to the dual binding conjugate, and (iii) administering the radionuclide coupled to the dual binding conjugate to the subject.

Claim 31 is directed to a conjugate consisting of (i) a radionuclide, (ii) an antibody, antibody fragment, or antibody construct, with affinity for a tumor associated antigen, and (iii) at least one non-cytotoxic folate.

The remaining claims depend from either claim 18 or 31.

### Rejection under 35 U.S.C. § 103(a)

Claims 18 and 25-35 are rejected under 35 U.S.C. § 103(a) as obvious over the combination of Wedeking and Sinkule. Claims 18, 25-28, and 30-35 are rejected under 35 U.S.C. § 103(a) as obvious over the combination of Wedeking and Goldenberg. These bases for the obviousness rejection are addressed, in turn, as follows.

*The Combination of Wedeking and Sinkule*

The Office states (page 3):

> Wedeking et al. (US 6,093,382) discloses the method of preparing a diagnostic/therapeutic gadolinium-folate (folic acid) conjugate and the method of targeting the diagnostic/therapeutic gadolinium-folate (folic acid) conjugate to a tumor cell expressing FBP (folate binding protein) (i.e. malignant cells).

And states (page 4):

> Sinkule et al. (EP 282057) discloses the method of monitoring the biodistribution of a receptor binding conjugate comprising three components, 1.) a monoclonal antibody, IgG 2.) a radionuclide [and 3.)] a chemotherapeutic agent, such as folate analogues and multiples thereof via administration to a mammalian (i.e. intravenous). (Citations omitted.)

With regard to combining the references, the Office states (pages 4 and 5):

> [I]t would have been obvious to one ordinarily skilled in the art to attach an antibody, such as the IgG of Sinkule et al. to the diagnostic/therapeutic gadolinium-folate (folic acid) conjugate of Wedeking et al. to target the conjugate specifically to a desired type of cancer cells/target. FBP is expressed in normal as well as different tumor cells and thus it would be advantageous to attach an antibody to the conjugate of Wedeking et al. to ensure site-specific targeting of the conjugate into the desired tumor cells with enhanced affinity while minimizing damage to normal cells.

Applicants respectfully disagree.

The determination whether an invention would have been obvious under 35 U.S.C. § 103 is a legal conclusion based on underlying findings of fact. *In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000). The factual determinations underpinning the legal conclusion of obviousness include 1) the scope and content of the prior art, 2) the level of ordinary skill in the art, 3) the differences between the claimed invention and the prior art, and 4) evidence of secondary factors, also known as objective indicia of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). A *prima facie* case of obviousness can only be established if one of ordinary skill in the art would have had a

reasonable expectation of success in making the proposed modification or combination. (M.P.E.P. § 2143.02). Applicants submit that the Office has failed to establish that, in combining the Wedeking and Sinkule, a skilled artisan would have had a reasonable expectation of success and, therefore, has failed to establish a *prima facie* case of obviousness.

Claim 18 recites a dual binding conjugate that can target malignant cells using both the antibody or antibody fragment moiety *and* the non-cytotoxic folate moiety. The conjugate of claim 31 also contains these two moieties. Both the non-cytotoxic folate and the antibody components of the conjugate target the conjugate to a malignant cell. In support of this statement, Applicants direct the Office's attention to Example 5 of the specification, which teaches that "[a]ntibodies labeled with folate can in principle react with both the antigen and folate binding protein, i.e., such conjugate possesses dual binding ability."

Wedeking describes targeting of small molecules (see for example, the molecules described at columns 27 to 32 of Wedeking) using a folate. Even when larger complexes of multiple chelating agents are used and several folates are required in Wedeking (e.g., columns 51 and 52) the molecular weight is fairly low (less than 5000 for the molecule at columes 51 and 52, adding around 450 with three gadoliniums complexed). The Office does not appear to distinguish an antibody from a small molecule moiety. Applicants note that the molecular weight of an IgG antibody is the order of 150,000 amu (atomic mass units). As such, an IgG antibody is thirty times larger than the largest complexes of Wedeking and three orders of magnitude larger than a folate. Given the vast size differences between a folate and an antibody, folate targeting and antibody targeting cannot simply be treated as if they are equivalent. Nothing in the combination of Wedeking with Sinkule teaches or suggests that the vanishingly small folate moiety (relative to an antibody) can have any useful positive effect in altering the distribution of a massive antibody or, conversely, that including an antibody in a complex, such as that

of Wedeking, that is targeted using a folate does not interfere with targeting by that folate.

In fact, Applicants submit that the information available in the art at the time of filing would have led the skilled worker away from combining a folate with an antibody for targeting a conjugate. At page 1, lines 22-27, the specification states:

> In a previous study, Shinoda et al. (1998) evaluated folate conjugated bovine serum albumin (BSA) labelled with the radionuclide indium-111, and found that there was a significant difference in pharmacokinetics and biodistribution of non-folate compared to folate labelled BSA. A high liver uptake and rapid blood clearance indicated that the folate labelled version of $^{111}$In-BSA was not particularly suitable for radionuclide delivery to tumour cells expressing folate binding protein.

Here, the art described in the specification indicates that adding a folate to a BSA-radionuclide complex is not particularly suitable for radionuclide delivery to tumor cells expressing folate binding protein. BSA with a mass of about 66,000 amu, like an antibody (150,000 amu for IgG), is a large protein, and Applicants submit that one skilled in the art would expect to observe similar results if a folate were added to an antibody-radionuclide complex. This teaching, is in direct contrast to the combination proposed by the Office. Applicants submit that the favorable distribution with a folate-antibody-radionuclide complex observed in the present application is unexpected in view of the knowledge in the art at the time of filing. One skilled in the art would not have had a reasonable expectation of success in combining the teachings of the cited references as proposed by the Office. The Office has failed to establish a *prima facie* case of obviousness for claims 18 and 25-35 over the combination of Wedeking and Sinkule. This basis for rejection should be withdrawn.

*The combination of Wedeking and Goldenberg*

The Office cites Wedeking for the reasons described above and combines this reference with Goldenberg for the following reasons (pages 5 and 6).

> Goldenberg et al. (US 5,698,178) discloses the method of selectively targeting diagnostic and therapeutic agents to multidrug resistant cells via administration of receptor binding conjugates. The receptor binding conjugates comprise various antibodies … at least one diagnostic or therapeutic agent, such as radionuclides and cancer chemotherapeutic drugs, such as folic acid analogues. (Citations omitted.)
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> [I]t would have been obvious to one ordinarily skilled in the art to attach an antibody, such as the IgG of Goldenberg et al. to the diagnostic/therapeutic gadolinium-folate (folic acid) conjugate of Wedeking et al. to target the conjugate specifically to a desired type of cancer cells/target.

Applicants again note that the antibody moiety is treated as equivalent to the folate moiety without any consideration as to whether these moieties are at all compatible. As explained above, adding a folate to a complex containing BSA and a radionuclide negatively affected its biodistribution and resulted in clearance by the liver. Nothing in Wedeking or Goldenberg teaches or suggests a beneficial targeting effect of combining a non-cytotoxic folate and an antibody to target a conjugate to malignant cells.

There simply is no reason provided in the combination of Wedeking with Goldenberg for one skilled in the art to generate the conjugates recited in Applicants' claims, much less an expectation of success in maintaining the binding (and therefore targeting) affinities of both the antibody and non-cytotoxic folate components of the conjugate. Applicants respectfully request that the obviousness rejection of claims 18, 25-28, and 30-35 over Wedeking and Goldenberg also be withdrawn.

## CONCLUSION

Applicants submit that the application is now in condition for allowance, and such action is hereby respectfully requested.

Enclosed are a Petition to extend the period for replying to the Office Action for three (3) months, to and including October 9, 2009, and an authorization to charge the required extension fee to Deposit Account No. 03-2095.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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